I. STUDIES ON THE METHYLATION OF AMINOALKYLTETRAHYDROQUINOLINES

II. REACTIONS OF ISOQUINOLINIUM COMPOUNDS WITH ANIONIC REAGENTS

BY

HARRY ALBERT DEWALT, JR.

A.B., Temple University, 1947
A.M., University of Illinois, 1948

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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I. STUDIES ON THE METHYLATION OF AMINOALKYLTETRAHYDROQUINOLINES

Introduction

The patent literature (1) describing the reaction between quinoline methosulfate with nitromethane and alkali postulated the formation of 1-methyl-2-nitromethyl-1,2,-dihydroquinoline. If introduction of the nitromethyl group did occur at the 2-position rather than the 4-position of the quinoline nucleus, the product should be convertible to 1-methyl-2-aminomethyl-1,2,3,4-tetrahydroquinoline by hydrogenation and to 1-methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline by subsequent methylation. Comparison of these compounds with those obtained from the catalytic reduction of 1-benzoyl-2-cyano-1,2-dihydroquinoline followed by hydrolysis of the benzoyl group and methylation would serve to establish their structures.

Rupe and coworkers (2) catalytically reduced 1-benzoyl-2-cyano-1,2-dihydroquinoline to 2-benzoylaminomethyl-1,2,3,4-tetrahydroquinoline; and hydrolysis followed by methylation with three mole equivalent of methyl iodide and potassium hydroxide gave three compounds: 1-methyl-2-aminomethyl-1,2,3,4-tetrahydroquinoline, 1-methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline and its methiodide.

Leubner (3), in an attempt to duplicate Rupe's experiments, heated 2-aminomethyl-1,2,3,4-tetrahydroquinoline with the required amount of methyl iodide and potassium hydroxide. The hydriodide of 1-methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline and a dimethylated amine which could be either 2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline or 1 - methyl - 2 - methylaminomethyl-1,2,3,4-tetrahydroquinoline were the only products isolated.

Discussion of Results

The structure of the dimethylated amine isolated by Leub-

ner (3) was established by the unequivocal synthesis of 1-methyl-2-methylaminomethyl-1,2,3,4-tetrahydroquinoline. This synthesis was initiated by the methylation of 2-benzoylaminomethyl-1,2,3,4-tetrahydroquinoline with methyl iodide in methanol in the presence of sodium bicarbonate to give 1-methyl-2-benzoylaminomethyl-1,2,3,4-tetrahydroquinoline; the side chain methylation of this amide was accomplished by treating the sodium salt with methyl iodide followed by hydrolysis to give the desired amine. A negative comparison of the physical constants of the free amines and that of their picrates and monohydrobromides indicated that the amine obtained by Leubner was 2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline.

The synthesis of 1-methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline was accomplished by hydrolyzing 1-methyl-2-benzoylaminomethyl-1,2,3,4-tetrahydroquinoline to the free amine; methylation with methyl iodide in methanol containing sodium bicarbonate gave the free amine and its methiodide. The melting point of the monopicrate of this amine differed from that reported by Rupe *et. al.*

From these results and those of Leubner (3), it appears that in the N-methylation process the first and second methyl groups which enter the 2-aminomethyl-1,2,3,4-tetrahydroquinoline molecule necessarily become attached to the side-chain nitrogen, which is aliphatic and more basic (both as a primary and a secondary amine) than the 1-nitrogen.

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II. REACTIONS OF ISOQUINOLINIUM COMPOUNDS WITH ANIONIC REAGENTS

Introduction

Leonard and Leubner (1) in an attempt to synthesize 1-nitromethyl-2-methyl-1,2-dihydroisoquinoline by condensing nitromethane and 2-methylisoquinolinium iodide in the presence of base (2) encountered surprising results. When equivalent quantities of reactants were used, the monopricate and monohydrochloride of *bis*-[1-(2-methyl-1,2,-dihydroisoquinolyl)]-nitromethane were isolated and characterized. However, when two moles of base per mole of nitromethane and 2-methylisoquinolinium iodide were used a 9.0% yield of 2-nitronaphthalene was the only product isolated. This latter transformation involved opening of the isoquinoline ring, and it is of interest to investigate the possibility of increasing the yield of 2-nitronaphthalene as well as to extend the scope of the reaction to other anionic reagents.

Discussion of Results

1. The isoquinoline to naphthalene conversion was investigated and a method of combining reagents developed which gives a maximum of 25% yield of 2-nitronaphthalene. A nitrogen-containing compound, *bis*-[1-(2-methyl-1,2-dihydroisoquinolyl)]-nitromethane was also isolated as a pure substance. The influence of the strength of the base and the undesirable self condensation of nitromethane have been demonstrated.

An earlier rearrangement of N-methylpapaverinium iodide to 6,7,3,4′-tetramethoxy-2-phenyl-1-naphthol has been checked, and treatment of 2-[2′,4′-dinitrophenyl]-papaverinium iodide with excess base gave a stable intermediate which proved that the isoquinoline ring opened under these conditions. This latter reaction also indicates the most likely method of ring closure to give the naphthalene derivative.

A mechanism for these transformations, based on the observed experimental results, has been postulated.

2. The reaction product between quinoline methosulfate, nitromethane, and base has been identified as 1-methyl-4-nitromethylenequinolane. Its structure has been proved unequivocally by reduction of its monohydrobromide compound to an amine, which was found to be identical with that obtained by the reduction of N-methyl-4-cyanoquinolinium iodide. The mechanism of reaction has been shown to be similar to that of the formation of a cyanine dye leuco base, and was further substantiated by the isolation of 1,2-dimethyl-4-nitromethylenequinolane from treating N-methyl-2-methylquinolinium iodide with nitromethane and base. No product could be obtained from similar treatment at N-methyl-4-methylquinolinium iodide.

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VITA

The author was born on August 7, 1922, in Conshohocken, Pennsylvania. After graduating from the Conshochocken High School in 1940, he entered Temple University in Philadelphia, Pennsylvania. From 1943 to 1946 he served in the Army of the United States. Upon discharge from the Army he returned to Temple University and was awarded his Bachelor of Arts degree in June, 1947. He entered the Graduate College of the University of Illinois in September, 1947, and received a Master of Arts degree in August, 1948. He held the Eli Lilly fellowship for the academic year 1948-49 and the DuPont fellowship for the academic year 1949-50.

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